UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/944,493	08/22/2001	Susan Weinbach	ISIS-4823	9925

34138 7590 06/01/2004

COZEN O'CONNOR, P.C.
1900 MARKET STREET
PHILADELPHIA, PA 19103-3508

EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/944,493	WEINBACH ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11-12-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 3-8-04.

Claims 1 and 3-23 are pending in the instant application.

Response to Arguments and Amendments

Maintained Rejections

Claims 1 and 3-23 are rejected under 35 U.S.C. 103(a) as being unpatentable and Chen (USPN 6,458,383), Chen (USPN 5,508,040) and Bai (5,840,329), in view of Friedman (USPN 6,309,853), Cochrum (USPN 5,876,742), Robinson (WO 85/02092) and Baracchini (USPN 5,801,154) for the reasons of record set forth in the Office action mailed 10-7-03.

Applicant's arguments filed 3-8-04 have been fully considered but they are not persuasive. Applicants argue that the references relied upon for the instant obviousness rejection do not render the instant invention obvious because Chen ('383) does not disclose two populations of oligonucleotide-containing particles in its delayed release oral formulation for enhanced intestinal absorption. Applicants are correct that Chen does not disclose two populations of oligonucleotide-containing particles in its delayed release oral formulation for enhanced intestinal absorption, but Chen was not cited as a single reference that anticipates the claimed invention. Rather, the combined teachings cited in the instant rejection illustrate that both the motivation and the means of the instant invention were obvious to one of ordinary skill in the art at the time the invention was made, as elaborated below.

Applicants assert that even if oligonucleotides were disclosed by Chen, there is insufficient motivation in Chen ('383) to render the instant invention obvious because the instant application discloses a specific solution to a problem (e.g. by providing various populations of carrier particles comprising a penetration enhancer and a delayed release coating or matrix for release of a pharmaceutical agent at a second location in the intestine). Contrary to Applicants' assertions, Chen ('383) teaches an analogous approach as that set forth in the instant application in addressing the general problem of limited drug delivery of pharmacological agents following enteral (e.g. oral) administration. Chen ('383) approaches this problem of limited drug absorption via enteral administration in a manner analogous to the instant disclosure: by providing enhanced intestinal absorption of pharmacological agents using penetration enhancers in combination with surfactants for either sustained release or delayed release in lower parts of the intestinal tract (e.g. see col. 7 and 8 of Chen). The term controlled release, according to Chen ('383), refers to immediate as well as non-immediate release formulations, with non-immediate release formulations including, but not limited to, sustained release and delayed release formulations. Delayed release, according to Chen ('383), refers to a delay in the release of a pharmaceutical composition from a dosage form following oral administration such that the majority of the composition is released in the lower GI tract. Furthermore, the dosage forms taught by Chen ('383) have enhanced transmembrane absorption compared to hydrophilic drug administration in the absence of penetration enhancers (which, according to both Chen and the instant application, include bile salts) and at least one surfactant. Chen ('383) teaches a

practical, effective, stable and non-invasive oral dosage form for delivering effective levels of pharmaceutical agents using enhancing compositions (including a delayed release fashion of delivery to a target site within the body, capable of making use of the enormous absorbing surface of the intestinal tract to improve the absorption enhancing index of pharaceutical compositions). In addition, Chen ('383) describes enteric coatings for controlled drug release (e.g. see col. 2), so that drug release is accomplished at a location in the lower intestinal tract below the point at which drug release would occur without the enteric coating. Chen ('383) also describes multiple enteric coatings targeted to release an active agent at various regions in the lower gastrointestinal tract for more effective and sustained delivery throughout the lower gastrointestinal tract. Likewise, the instant disclosure addresses the general problem of enhancing intestinal absorption of drugs by enteric (oral) administration utilizing delayed release oral formulations for enhanced lower intestinal drug absorption (e.g. see page 2 of the instant specification).

Applicants argue that Chen ('383) is clearly directed to compositions for the delivery of low molecular weight heparins with no suggestion at all of oligonucleotides. Applicants' assertions are partially correct; Chen ('383) does not explicitly disclose the term oligonucleotides. Chen, however, teaches oral formulations for the enhanced delivery of hydrophilic pharmaceutical agents (e.g. with an aqueous solubility greater than ~100 ug/ml), which pharmaceutical agents include macromolecular drugs such as peptides, proteins, peptidomimetics, nucleotides, nucleosides, genetic materials... (see col. 8, lines 53-59 of Chen '383)). Oligonucleotides are generally recognized as genetic

materials in the art, and have a solubility within the range of hydrophilic drugs disclosed by Chen. Likewise, the instant disclosure teaches an invention for enhancing the intestinal absorption of a variety of pharmaceutical agents, which agents include proteins, peptides, nucleic acids, oligonucleotides, peptide hormones, chemotherapeutic agents (see page 2 of the instant specification and original claim 1). The instant disclosure and Chen ('383) therefore address the same problem: the limited effective intestinal delivery of pharmaceutical agents following oral administration. The instant disclosure and Chen ('383) utilize the same approach to this problem: enhancing intestinal absorption in the lower GI tract using absorption enhancing compositions. In addition, both Friedman ('853, esp. at col. 17, 28-29, 43-45, teaching delayed release particles for enhanced antisense oligonucleotide oral delivery) and Baracchini ('154 esp. at col. 3-4, teaching the oral administration of antisense oligonucleotides) teach the motivation and means for orally administering oligonucleotides.

Applicants argue that the disclosures of Chen ('040) and Bai ('329) do not cure the deficiencies of Chen ('383) because Chen ('040) and Bai do not explicitly articulate the term *penetration enhancers*, nor do they include oligonucleotides in their formulations. Applicants are correct in their assertion that the term *penetration enhancer* is not explicitly mentioned in Bai or Chen ('040). But the instant application defines penetration enhancers as including a broad array of compounds, including fatty acids, bile acids, chelating agents and non-chelating non-surfactants (see page 3 of the instant specification). Likewise, Bai teaches a plurality of particles for the immediate or sustained release of pharmaceutical agents, which particles include polymer-blend

hydrogels for the controlled release of protein and non-protein drug delivery, including particles with outer coatings containing water-insoluble, water-permeable polymers in various stoichiometries. (see '329, e.g. col. 3, 7-9). In addition, Chen ('040) teaches at least two different populations of drug delivery particles for enhanced therapeutic drug delivery to the GI tract (e.g. see figures 1-3; col. 3, esp. at lines 37-60), which particles comprise penetration enhancers including fatty acids, waxes and salts thereof (see col. 3, esp. at lines 37-60). The compositions of these delivery particles disclosed by Bai and Chen ('040) for enhanced drug delivery therefore include compositions that are encompassed within the instant application's definition of penetration enhancers. So, contrary to Applicants' assertions, Bai and Chen ('040) both teach the motivation to enhance drug delivery in an organism using different populations of delivery particles comprising penetration enhancers.

Therefore, the instant rejection for obviousness is maintained for all the reasons stated above.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

5-25-04

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
5/24/04